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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/919,347	07/31/2001	Noel John de Souza	U 013560-1	2749
140	7590	01/31/2005	EXAMINER	
LADAS & PARRY 26 WEST 61ST STREET NEW YORK, NY 10023			SEAMAN, D MARGARET M	
			ART UNIT	PAPER NUMBER
			1625	

DATE MAILED: 01/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/919,347

Applicant(s)

DE SOUZA ET AL.

Examiner

D. Margaret Seaman

Art Unit

1625

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 September 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 198-325 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 198-325 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This case was filed 7/31/01 and claims benefit of Provisional Applications 60/222201 (8/1/00), 60/286291 (4/25/01) and 60/287104 (4/27/01). RCE papers were filed 5/17/04 and a response to the last office action was filed 9/9/2004. Claims 1-197 have been canceled. Claims 198-325 are before the Examiner.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 198-325 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are ambiguous due to the variable "n" being defined differently 3 times in the claims. It is suggested that the variable "n" be changed to three different moieties (such as n, p and q) so that each variable has only one definition.

The claims are ambiguous due to the definition of the variable R₇. R₇ is defined as being (see claim 198 page 3 line 25 of the amendment) wherein the R₇ moiety is linked to 2 core molecules of the formula I to form a bis compound. However, the

claims do not fully describe where/how the two core molecules are connected or what part of formula I is the core.

Claims 202-294 and 301 are ambiguous due to the claims not defining R4, R4a or R6.

The claims are ambiguous due to the moiety "Structure I" being different for claim 198 and 202. Which figure is "structure I" and which should be of a different name?

Claims 322-325 are ambiguous due to the Method claims being dependent from Compound claims.

Correction is required.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 198-294, 298-299, 301, 303, 305-309, 312-313, 315 and 317-325 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification does not enable the ordinary artisan to make or use the instant

compounds or methods when R₇ is a bis compound linked to 2 core molecules of the formula I

6. Claims 198-294, 298-299, 301, 303, 305-309, 312-313, 315 and 317-325 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant specification does not adequately describe the compound wherein R₇ is a bis compound linked to 2 core molecules of the formula I. How is the connection made? What part of the formula I is the "core"? Can part of R₇ be substituted by a compound of formula I and therefore become part of the bis compound? This is what is not fully described within the instant specification. It is not seen where the instant specification adequately describes the R₇ moiety when it is other than Br, F or NR₉R₁₀.

7. Claims 198-294, 298-299, 301, 303, 305-309, 312-313, 315 and 317-325 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue".

These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

- 1) The breadth of the claims,
- 2) The nature of the invention,
- 3) The state of the prior art,
- 4) The level of one of ordinary skill,
- 5) The level of predictability in the art,
- 6) The amount of direction provided by the inventor,
- 7) The existence of working examples,
- 8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The nature of the invention is the method of treating a microbial infection and compounds that are efflux pump inhibitors.

The state of the prior art: The state of the prior art knows of other quinolone compounds that treat microbial infections (with or without those compounds being EPIs). However, the existence of bis quinoline compounds is not known in the art.

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In *re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

The presence or absence of working examples: The compounds shown to work of the instant specification are compounds that do not have the bis quinoline attached through the R7 moiety.

The amount of direction or guidance present: The guidance present in the specification is that the compounds having R7 being Br, F or NR⁹R¹⁰ work as EPIs and treat microbial infections. Compounds having R7 being a moiety that is linked to 2 core molecules of the Formula I have not been made or tested.

The breadth of the claims: The claims are drawn compounds and to the treatment of microbial infections by compounds of formula I.

The quantity of experimentation needed: The quantity of experimentation needed is undue. One skilled in the art would need to determine what is the linkable between R7 and the second (or third) core molecule s of formula I because it is unclear as to whether R7 is linked to 2 more molecules of formula I or if R7 links two core molecules.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro

and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compounds of formula I wherein R_7 is other than Br, F or NR_9R_{10} for the treatment of microbial infections. As a result necessitating one of ordinary skill to perform an exhaustive search for which compounds can treat the infection in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, one of ordinary skill in the art would have to engage in undue experimentation to test which compounds are encompassed by the instant claims and which compounds can treat microbial infections.

This rejection can be overcome by deleting part of the definition of R_7 .

Claim Rejections - 35 USC § 102/103

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

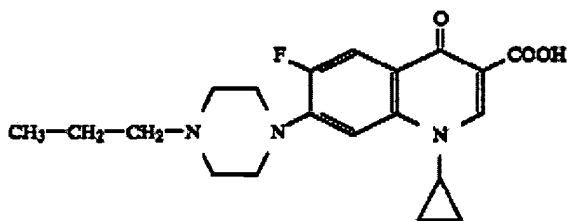
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

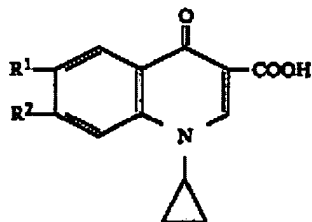
10. Claims 298, 299, 301, 303, 305-309, 312-313 and 315 are rejected under 35 U.S.C. 102(b) as being anticipated by Grohe (US Patent #4,563,459).

Grohe teaches the first compound of column 9 that anticipates claims 301, 305-309, 312, 313 and 315. This compound is



and anticipates the instant claims due to the claims being drawn to either compounds or pharmaceutical compositions of compounds.

Grohe teaches also compound 25 column 25 which is

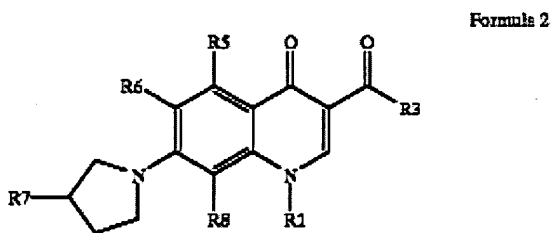


Example No.	R ¹	R ²
25	H	

and this compound anticipates the instant claims 298, 299, 303, 305-309, 312, 313 and 315.

11. Claims 202-294 and 320 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Ledoussal (US Patent # 6,329,391).

Ledoussal teaches



In the following examples, R₁ is cyclopropyl, R₂ is hydroxy,

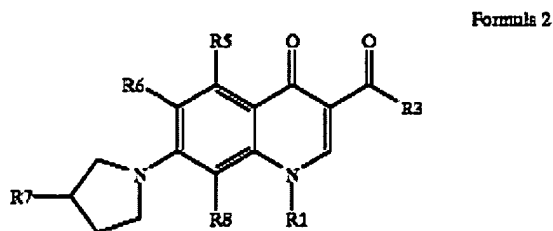
Example	R5	R6	R7	R8
1	-NH ₂	H	-NH ₂	Cl
2	-NH ₂	H	-CH ₂ NH ₂	Cl
3	-NH ₂	H	-CH(CH ₃)NH ₂	Cl
4	F	H	-NH ₂	Cl
5	F	H	-CH ₂ NH ₂	Cl
6	F	H	-CH(CH ₃)NH ₂	Cl
7	-OCH ₃	H	-NH ₂	Cl
8	H	H	-CH ₂ NH ₂	CH ₃
9	H	H	-CH(CH ₃)NH ₂	CH ₃
10	-OH	H	-NH ₂	Cl
11	-OH	H	-CH ₂ NH ₂	Cl
12	-OH	H	-CH(CH ₃)NH ₂	Cl
13	H	H	-NH ₂	Cl
14	H	H	-CH ₂ NH ₂	Cl
15	H	H	-CH(CH ₃)NH ₂	Cl
16	H	H	-NH ₂	OCH ₃
17	H	H	-CH ₂ NH ₂	OCH ₃

example 16 that fully anticipates compounds encompassed by the method of treatment claims. Ledoussal teaches that these compounds treat microbial infections. Due to this, the method of treatment claims 202-294 and 320 are inherently encompassed.

For 103 purposes, the difference between Ledoussal and the instant method claims is that Ledoussal teaches the compounds as treatments for microbial infections. The instant claims are drawn to a method of suppressing growth of a microbe expressing an efflux pump. However, the end result is that the compounds encompassed by the instant claims and the compounds taught by Ledoussal both treat microbial infections. The compounds used are the same and the end result is the same. Therefore, the methods are obvious variants of each other.

12. Claims 298-299, 301, 303, 305-309, 312, 313 and 315 are rejected under 35 U.S.C. 102(b) as being anticipated by Ledoussal (US Patent #6,329,391).

Ledoussal teaches



In the following examples, R_1 is cyclopropyl, R_3 is hydroxy,


Example	R_5	R_6	R_7	R_8
1	$-\text{NH}_2$	H	$-\text{NH}_2$	Cl
2	$-\text{NH}_2$	H	$-\text{CH}_2\text{NH}_2$	Cl
3	$-\text{NH}_2$	H	$-\text{CH}(\text{CH}_3)\text{NH}_2$	Cl
4	F	H	$-\text{NH}_2$	Cl
5	F	H	$-\text{CH}_2\text{NH}_2$	Cl
6	F	H	$-\text{CH}(\text{CH}_3)\text{NH}_2$	Cl
7	$-\text{OCH}_3$	H	$-\text{NH}_2$	Cl
8	H	H	$-\text{CH}_2\text{NH}_2$	CH_3
9	H	H	$-\text{CH}(\text{CH}_3)\text{NH}_2$	CH_3
10	$-\text{OH}$	H	$-\text{NH}_2$	Cl
11	$-\text{OH}$	H	$-\text{CH}_2\text{NH}_2$	Cl
12	$-\text{OH}$	H	$-\text{CH}(\text{CH}_3)\text{NH}_2$	Cl
13	H	H	$-\text{NH}_2$	Cl
14	H	H	$-\text{CH}_2\text{NH}_2$	Cl
15	H	H	$-\text{CH}(\text{CH}_3)\text{NH}_2$	Cl
16	H	H	$-\text{NH}_2$	OCH_3
17	H	H	$-\text{CH}_2\text{NH}_2$	OCH_3

example 16 that fully anticipates compounds of claims 298-299, 301, 303, 305-309, 312, 313 and 315.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. Margaret Seaman whose telephone number is 571-272-0694. The examiner can normally be reached on 630am-4pm, First Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecelia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


D. Margaret Seaman
Primary Examiner
Art Unit 1625

dms